OIPE JC97 OCT 11 2002 PATENT & TRADEMARK OFFICE

Attorney Docket No.: 04734.0003
Customer Number 22,852

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hartmut STROBEL et al.

Serial No.: **10/073,160**

Filed: **February 13, 2002**

For: **ACYLATED INDANYL AMINES AND THEIR USE AS PHARMACEUTICALS**

Group Art Unit: **1614**

Examiner: **Not Yet Assigned**

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

CLAIM FOR PRIORITY

Under the provisions of 35 U.S.C. § 119, applicants hereby claim the benefit of the filing date of European Patent Application No. 01102850.3, filed February 13, 2001, for the above-identified U.S. patent application.

In support of this claim for priority, enclosed is one certified copy of the priority application.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: October 11, 2002

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Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

01102850.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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THE HAGUE, 29/04/02
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 01102850.3
Demande n°:

Anmeldetag:
Date of filing: 13/02/01
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
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Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Acylated indanyl amines and their use as pharmaceuticals

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
C07C233/64, C07C235/44, C07D213/56, C07D307/78, C07D317/60, C07D333/24, A61K31/165, A61K31/36, A61K31/38, A61K31/435, A61P9/00

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing:
Etats contractants désignés lors du depôt: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR

Bemerkungen:
Remarks:
Remarques:

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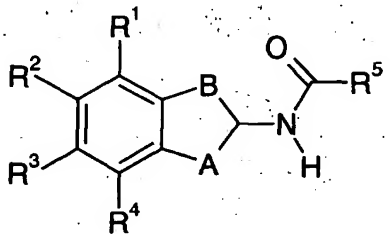
EPO - Munich
67
13. Feb. 2001

Aventis Pharma Deutschland GmbH

February 13, 2001
APD61815EP IB/HN/uw

Acylated indanyl amines and their use as pharmaceuticals

The present invention relates to acylated indanyl amines of the general formula (I) with the definitions of R^1 to R^5 and A and B given below in the text, and/or a pharmaceutically acceptable salts thereof, and their use as pharmaceutical agents.



(I)

Endothelial NO synthase (eNOS, NOS-III) belongs to a group of three isoenzymes which produce nitric oxide (NO) by oxidation of arginine. Endothelially released NO is of central importance in a number of key cardiovascular mechanisms. It has a vasodilating effect and inhibits the aggregation of platelets, the adhesion of leukocytes to the endothelium and the proliferation of intimal smooth muscle cells.

Endothelial NO synthase is subject to physiological and pathophysiological regulation both at the transcriptional and at the post-transcriptional level. Enzyme already present in the endothelium may undergo calcium-dependent and calcium-independent activation through phosphorylation of specific amino acids, but also by direct interactions with specific proteins. Stimulators of this, usually transient, NO release are, extracellular arginine, 17β-estrogen and the mechanical stimulus exerted on the luminal surface of the endothelium by the blood flow (shear stress). The latter additionally leads to regulation of eNOS at the transcriptional level. Thus, for example, Sessa et al. (Circ. Research 74 (1994) 349-353) were able by means of exercise training and the increase in shear stress associated therewith to obtain a marked increase in ecNOS.

Whether regulation at the post-transscriptional level is relevant in vivo, is not unambiguously proved. Thus, for example, administration of a high arginine dose is followed by only a transient improvement in the endothelium-dependent vasorelaxation in patients with coronary heart disease.

On the other hand, the significance of the upregulation of the eNOS protein is scientifically accepted. Thus, there are findings which show that the protective properties of the HMG-CoA reductase inhibitor simvastatin can be attributed, besides the lipid lowering, also in part to an increase in eNOS expression in vivo (Endres et al., Proc. Natl. Acad. Sci. USA 95 (1998) 8880-8885). It is additionally known that single point mutations in the 5'-flanking region of the eNOS gene ("eNOS promoter"), and the reduction in the rate of eNOS gene transcription associated therewith, in the Japanese population is associated with an increase in the risk of coronary spasms (Nakayama et al., Circulation 99 (1999) 2864-2870).

The current assumption therefore is that the transcriptional and post-transcriptional mechanisms of eNOS regulation are seriously disturbed in a large number of disorders, especially in cardiovascular disorders. Even in very early stages of a wide variety of cardiovascular disorders it is possible for a dysfunction of this type in the endothelium lining the blood vessels to lead to a deficiency of bioactive NO, which is manifested as the disorder progresses in the form of measurable pathophysiological and morphological changes. Thus, critical steps in early atherogenesis are speeded up by a decrease in endothelial NO release, such as, for example, the oxidation of low density lipoproteins, the recruitment and deposition of monocytes in the intima of vessels, and the proliferation of intimal cells. A consequence of atherogenesis is the formation of plaques on the inside of the blood vessels, which may in turn lead, through a diminution in the shear stress, to a further decrease in endothelial NO release and a further deterioration in the pathology. Since endothelial NO is also a vasodilator, a decrease thereof frequently also leads to hypertension, which may, as an independent risk factor, cause further organ damage.

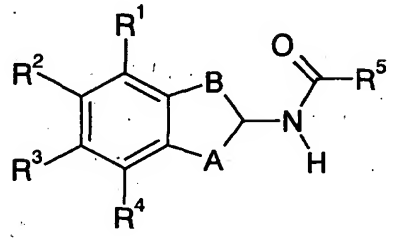
The aim of a therapeutic approach to the treatment of these disorders must accordingly be to interrupt this chain of events by increasing the endothelial NO expression. Gene transfer experiments which lead in vitro to overexpression of NO synthase in previously damaged vessels are in fact able to counteract the described processes and are thus evidence of the correctness of this approach (Varenne et al., Hum. Gene Ther. 11 (2000) 1329).

Some low molecular weight compounds which, in cell cultures, may lead to a direct effect on eNOS transcription and expression are disclosed in the literature. The statins which have already been mentioned are, however, the only substances for which it has been possible to date to show such an increase in eNOS in vivo as a side effect. In view of the known range of side effects of this class of substances, however, it is unclear how far this effect is present in a toxicologically unproblematic dose.

Liao et al. claim in WO 99/47153 and WO 00/03746 the use of rhoGTPase inhibitors and agents which influence the organization of the actin cytoskeleton for increasing eNOS in endothelial cells and for the therapy of various disorders such as, for example, strokes or pulmonary hypertension, without, however, indicating a specific way of achieving this.

Thus, there exists a strong need for compounds which upregulate eNOS-expression in endothelial cells. The object of the present invention is to provide compounds showing this ability.

This object is attained by acylated indanyl amines or a pharmaceutically acceptable salt thereof according to the general formula (I).



(I)

In the above formula,

R^1 and R^4 are independently from each other selected from the group consisting of:

H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^9CO; $CONR^{10}R^{11}$; $COOR^{12}$; CF_3; halogenes; pseudohalogenes; $NR^{13}R^{14}$; OR^{15}; $S(O)_mR^{16}$; $SO_2NR^{17}R^{18}$; and NO_2;

R^2 and R^3 are independently from each other selected from the group consisting of: H; halogenes; pseudohalogenes; unsubstituted and at least monosubstituted C_1-C_6-alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_6-alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3; CN; NO_2; (C_1-C_6-alkyl)amino; di(C_1-C_6-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O-; unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1-C_3-alkyl, halogenes and methoxy;

A is CH_2, CHOH or CH-(C_1-C_3-alkyl);

B is CH_2 or CH-(C_1-C_3-alkyl);

R^5 is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogenes; pseudohalogenes; C_1-C_{10}-alkyl; C_3-C_5-alkandiyl; phenyl; phenylsubstituted C_1-C_4-alkyl; CF_3; OH; C_1-C_{10}-alkoxy; phenoxy; benzyloxy; CF_3O; (C_1-C_{10}-alkyl)COO; $S(O)_mR^{20}$; (C_1-C_{10}-alkyl)amino; di(C_1-C_{10}-alkyl)amino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_3-alkyl)-; (C_1-C_{10}-alkyl)-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; phenylamino; phenyl-CO; $COOR^{21}$; $CONR^{22}R^{23}$; $SO_2NR^{24}R^{25}$; and aromatic or aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, O and S which can be substituted by one or more substituents from the group consisting of halogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; wherein all phenyl groups and phenyl-containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3;

R^6 is H, C_1-C_6-alkyl or benzyl;

R^7 is selected from the group consisting of:
H; C_1-C_6-alkyl which can be phenyl-substituted; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or

more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

R^8 is H or C_1-C_6-alkyl;

R^9 is C_1-C_6-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogenes, pseudohalogenes, and CF_3;

R^{10} independently has the same meaning as R^7;

R^{11} independently has the same meaning as R^8;

R^{12} independently has the same meaning as R^6;

R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{14} is H or C_1-C_6-alkyl;

R^{15} is selected from the group consisting of: H; C_1-C_6-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{16} is selected from the group consisting of: C_1-C_6-alkyl; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substitutents can be present;

R^{17} independently has the same meaning as R^7;

R^{18} independently has the same meaning as R^8;

R^{19} independently has the same meaning as R^{16};

R^{20} independently has the same meaning as R^{16};

R^{21} independently has the same meaning as R^{6};

R^{22} independently has the same meaning as R^{7};

R^{23} independently has the same meaning as R^{8};

R^{24} independently has the same meaning as R^{7};

R^{25} independently has the same meaning as R^{8};

heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O and S;

aryl is phenyl, naphth-1-yl or naphth-2-yl;

m is 0, 1 or 2,

with the proviso that, in case R^1, R^2, R^3 and R^4 are all H, R^5 is not phenyl, 5-chloro-2-ethoxyphenyl, 5-chloro-2-methoxyphenyl, 5-bromo-2-methoxyphenyl; or quinoxalin-2-yl; in case R^5 is phenyl, A is not CHOH, R^1 is not methoxy or methyl, R^2 is not methyl or B is not $CH\text{-}CH_3$; in case R^2 is NO_2, R^5 is not 3-chlorophenyl.

If, in the compounds of formula (I), groups or substituents such as, for example, aryl, heteroaryl, alkyl etc., can be present several times, they all independently from each other have the meanings indicated and can hence, in each individual case, be identical with or different from each other. One example is the di(C_1-C_{10}-alkyl)amino group in which the alkyl substitutents can be identical or different.

Alkyl, alkenyl and alkynyl residues can be linear or branched, acyclic or cyclic. This also applies when they are part of other groups, for example in alkoxy groups, alkoxycarbonyl groups or amino groups, or when they are substituted.

Examples for alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these residues, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. The term alkyl here also expressly includes cycloalkyl residues and cycloalkyl-alkyl-residues (alkyl substituted by cycloalkyl) containing at least three carbon atoms. Examples for such cycloalkyl residues are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. All cycloalkyl groups can be substituted by one or more identical or different (C_1-C_4)-alkyl residues, in particular by methyl. Examples for substituted cycloalkyl residues are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-dimethylcyclopentyl. Furthermore, unless stated otherwise, the term alkyl here also includes unsubstituted alkyl residues as well as alkyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl groups. In substituted alkyl residues, for example arylalkyl, hydroxyalkyl such as -(C_1-C_3)-alkyl-OH or alkoxyalkyl such as -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl, the substituents can be present in any desired position.

Examples for alkenyl and alkynyl groups are the vinyl residue, the 1-propenyl residue, the 2-propenyl residue (allyl residue), the 2-butenyl residue, the 2-methyl-2-propenyl residue, the 3-methyl-2-butenyl residue, the ethynyl residue, the 2-propynyl residue (propargyl residue), the 2-butynyl residue or the 3-butynyl residue. The term alkenyl here also expressly includes cycloalkenyl residues and cycloalkenyl-alkyl-residues (alkyl substituted by cycloalkenyl) containing at least three carbon atoms. Examples for cycloalkenyl residues are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. All cycloalkenyl groups can be substituted by one or more identical or different (C_1-C_4)-alkyl residues, in particular by methyl. Furthermore, unless stated otherwise, the term alkenyl and alkynyl here also includes unsubstituted alkenyl and alkynyl residues as well as alkenyl and alkynyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl groups. In substituted alkenyl and alkynyl residues, for example arylalkenyl, hydroxyalkenyl such as -(C_2-C_3)-alkenyl-OH or alkoxyalkenyl such as (C_1-C_3-alkyl)-O-(C_2-C_4-alkenyl)-, the substituents can be present in any desired position.

Examples for C_3-C_5-alkandiyl are $-CH_2CH_2CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2-$ groups.

If not stated otherwise, the above-mentioned phenyl residues, naphthyl and indanyl residues and heterocyclic residues can be unsubstituted or can carry one or more, for example one, two, three or four, of the substituents indicated in the above definition which

can be in any desired position. If in compounds of the formula (I) nitro groups are present as substituents, in total only up to two nitro groups are preferably present in the molecule. In monosubstituted phenyl residues the substituent can be in the 2-position, the 3-position or the 4-position, in disubstituted phenyl residues the substituents can be in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl residues the substituents can be in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. In fourfold substituted phenyl residues, the substituents can be in the 2,3,4,5-position, the 2,3,4,6-position, or the 2, 3,5,6-position. Tolyl (= methylphenyl) can be 2-tolyl, 3-tolyl or 4-tolyl. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl residues the substituent can be in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position, in monosubstituted 2-naphthyl residues in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In higher substituted naphthyl radicals, for example 1-naphthyl radicals or 2-naphthyl radicals which carry two or three substituents, the substituents can also be situated in all possible positions. Indanyl residues include indan-1-yl residues and indan-2-yl residues which can be unsubstituted or carry one or more of the substituents indicated. In case the indanyl residues are substituted, the substituent or substituents can be in any of the positions possible.

The above definitions as well as the following definitions relating to monovalent residues equally apply to the divalent residues phenylene, naphthylene and heteroarylene. Those divalent residues can be attached to the adjacent groups by any ring carbon atom. In the case of a phenylene residue, these can be in 1,2-position (ortho-phenylene), 1,3-position (meta-phenylene) or 1,4-position (para-phenylene). In the case of a naphthylene residue the free bonds can be in 1,2-position (= 1,2-naphthylene or 1,2-naphthalinediyl) or in 1,3-position, 1,4-position, 1,5-position, 1,6-position, 1,7-position, 1,8-position, 2,3-position, 2,6-position or 2,7-position. In the case of 5-membered ring aromatics containing one heteroatom such as, for example, thiophene or furan, the two free bonds can be in 2,3-position, 2,4-position, 2,5-position or 3,4-position. A divalent residue derived from pyridine can be a 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-pyridinediyl residue. In the case of unsymmetrical divalent residues the present invention includes all positional isomers, i. e., in the case of a 2,3-pyridinediyl residue, for example, it includes the compound in which the one adjacent group is present in the 2-position and the other adjacent group is present in the 3-position as well as the compound in which the one adjacent group is present in the 3-position and the other adjacent group is present in the 2-position.

Unless stated otherwise, heteroaryl residues, heteroarylene residues, heterocyclyl residues and rings which are formed by two groups bonded to a nitrogen are preferably derived from heterocycles which contain one, two, three or four heteroatoms which can be identical or different; more preferably they are derived from heterocycles which contain one, two, or three, in particular one or two, heteroatoms which can be identical or different. Unless stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably they are monocyclic or bicyclic. The rings preferably are 5-membered rings, 6-membered rings or 7-membered rings. Examples of monocyclic and bicyclic heterocyclic systems from which residues occuring in the compounds of the formula (I) can be derived, are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole (= oxazole), 1,2-oxazole (= isoxazole), 1,3-thiazole (= thiazole), 1,2-thiazole (= isothiazole), tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridin, or phenothiazine, each of them in saturated form (perhydro form) or in partially unsaturated form (for example in the dihydro form or the tetrahydro form) or in maximally unsaturated form, in case the respective forms are known and stable. Thus, suitable heterocycles also include, for example, the saturated heterocycles pyrrolidine, piperidine, piperazine, morpholine and thiomorpholine. The degree of saturation of heterocyclic groups is indicated in their individual definitions. Unsaturated heterocycles can contain, for example, one, two or three double bonds within the ring system. 5-membered rings and 6-membered rings can in particular also be aromatic.

Substituents which may be derived from these heterocycles can be attached via any suitable carbon atom. Residues derived from nitrogen heterocycles can carry a hydrogen atom or a substituent on a ring nitrogen atom, and examples include pyrrole, imidazole, pyrrolidine, morpholine, piperazine residues, etc. Those nitrogen heterocyclic residues can also be attached via a ring nitrogen atom, in particular if the respective heterocyclic residue is bonded to a carbon atom. For example, a thienyl residue can be present as 2-thienyl residue or 3-thienyl residue, a furyl residue as 2-furyl residue or 3-furyl residue, a pyridyl residue as 2-pyridyl residue, 3-pyridyl residue or 4-pyridyl residue, a piperidinyl residue as 1-piperidinyl residue (= piperidino residue), 2-piperidinyl residue, 3-piperidinyl residue or 4-piperidinyl residue, a (thio)morpholinyl residue as 2-(thio)morpholinyl

residue, 3-(thio)morpholinyl residue or 4-(thio)morpholinyl residue (= thiomorpholino residue). A residue derived from 1,3-thiazole or imidazole which is attached via a carbon atom can be attached via the 2-position, the 4-position or the 5-position.

In case a heterocyclic groups is substituted, it can carry one or more, for example one, two, three or four, identical or different substituents. Substituents in heterocycles can be present in any desired positions, for example in a 2-thienyl residue or 2-furyl residue in the 3-position and/or in the 4-position and/or in the 5-position, in a 3-thienyl residue or 3-furyl residue in the 2-position and/or in the 4-position and/or in the 5-position, in a 2-pyridyl residue in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 3-pyridyl residue in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 4-pyridyl residue in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position. Suitable nitrogen heterocycles can also be present as N-oxides or as quarternary salts containing a counterion which is derived from a pharmaceutically acceptable acid. Pyridyl residues, for example, can be present as pyridine-N-oxides.

Halogen is fluorine, chlorine, bromine oder iodine, preferably fluorine or chlorine.

Examples for pseudohalogenes are CN and N_3, a preferred pseudohalogene is CN.

The present invention includes all stereoisomeric forms of the compounds of the formula (I). Centers of asymmetry that are present in the compounds of formula (I) all independently of one another have S configuration or R configuration. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the present invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. All these forms are an object of the present invention. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compounds of the formula (I) or at the stage of an

intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of formula (I).

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The present invention furthermore includes all solvates of compounds of the formula (I), for example hydrates or adducts with alcohols, active metabolites of the compounds of the formula (II), and also derivatives and prodrugs of the compounds of the formula (I) which contain physiologically tolerable and cleavable groups, for example esters, amides and compounds in which the N-H group depicted in formula (I) is replaced with an N-alkyl

group, such as N-methyl, or with an N-acyl group, such as N-acetyl or N-argininyl, including pharmaceutically acceptable salts formed on functional groups present in the N-acyl group.

Preferred compounds of the formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

In preferred embodiments of the present invention, the substituents R^1 to R^5, A and B and the groups aryl and heteroaryl of the formula (I) independently from each other have the following meanings. Hence, one or more of the substituents R^1 to R^5 and A and B can have the preferred or particularly preferred meanings given below.

R^1 is preferably selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogenes; pseudohalogenes; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^1 is in particular halogene or C_1-C_4-alkyl.

R^2 is preferably selected from the group consisting of: H; halogenes; pseudohalogenes; and C_1-C_3-alkyl.

R^3 and R^4 are preferably each H.

A is preferably selected from the group consisting of CH_2 and CHOH; A is in particular CH_2.

B is preferably selected from the group consisting of CH_2 and CH-CH_3; B is in particular CH_2.

R^5 is preferably selected from the group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_3-alkyl)amino-, di(C_1-C_3-alkyl)amino, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which

is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -OCH_2-CH_2-O-; unsubstituted and at least mono-halogene-substituted benzodioxolyl and dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-S(O)$_m$-, phenylmercapto, –O-CH_2-O-, –O-CF_2-O, and -O-CH_2-CH_2-O-; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-S(O)$_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -O-CH_2-CH_2-O-; R^5 is in particular selected from the group consisting of: 4-fluorophenyl; 4-chlorophenyl; 4-bromophenyl; 4-(C_1-C_3-alkyloxy)-phenyl; 4-trifluoromethoxyphenyl; 2-bromo-4-fluorophenyl; 2-chloro-4-fluorophenyl; 3,4-dimethylphenyl; 2,4-dimethylphenyl; 4-chloro-2-methylphenyl; 2-hydroxy-4-methylphenyl; 2-hydroxy-4-ethoxyphenyl; 2-methoxy-4-methylphenyl; 4-phenoxyphenyl; 3-fluoro-4-methylphenyl; benzo[1,3]dioxol-5-yl; 2,2-difluoro-benzo[1,3]dioxol-5-yl; 2,3-dihydrobenzofuran-5-yl; thienyl; halogene-substituted thienyl; 5-acetylthienyl; pyridyl; halogene-substituted pyridyl; and (C_1-C_3-alkyl)-substituted pyridyl.

Heteroaryl is preferably selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms from the group consisting of N, O, and S; heteroaryl is in particular selected from the group consisting of furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

Aryl is preferably phenyl.

m is preferably 0 or 2.

Compounds of the formula (I) in which all of the above-mentioned groups have the preferred meanings or the particularly preferred meanings defined above are also an object of the present invention.

The compounds according to general formula (I) and their precursors can be prepared according to methods published in the literature or, respectively, analogous methods. Appropriate methods have been published in, for example, Masui et al., Tetrahedron Lett. (1998) 39, Colette et al., Ann. Chim. (Paris) 1 (1976) 269, Cannon et al., J. Med. Chem. 15 (1972) 348, Cannon et al., J. Med. Chem. 25 (1982) 1442, US 4,192,88 and Crooks Chem.

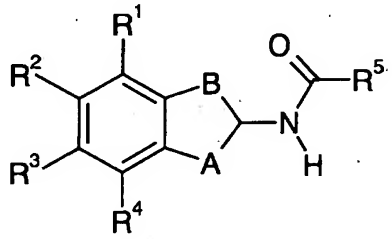
Ind. (London) 12 (1974) 495. Indanyl amines prepared according to the disclosed methods can be dissolved in a solvent like, for example, dichloromethane, THF, toluene or dioxane and reacted in the presence of base like, for example, triethylamine, with an appropriate carboxylic acid derivative, for example a carboxylic acid chloride. This reaction is preferably carried out at room temperature. Alternatively, the compounds according to the general formula (I) are obtained by a coupling reaction of the respective indanyl amine with an acid, which indanyl amine and/or acid may be substituted and/or functionalized, in the presence of a base like, for example, diisopropylethylamine, and the use of an appropriate coupling reagent like, for example, carbodiimides, HATU or TOTU. The thus obtained acyl indanyl amines can then be functionalized, in order to obtain further desired compounds according to the general formula (I). The reaction leading to the above-mentioned acyl indanyl amines and the reactions used in the functionalization are known to the person skilled in the art.

All reactions for the synthesis of the compounds of the formula (I) are per se well-known to the skilled person and can be carried out under standard conditions according to or analogously to procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. Depending on the circumstances of the individual case, in order to avoid side reactions during the synthesis of a compound of the formula (I), it can be necessary or advantageous to temporarily block functional groups by introducing protective groups and to deprotect them in a later stage of the synthesis, or introduce functional groups in the form of precursor groups which in a later reaction step are converted into the desired functional groups. Such synthesis strategies and protective groups and precursor groups which are suitable in an individual case are known to the skilled person. If desired, the compounds of the formula (I) can be purified by customary purification procedures, for example by recrystallization or chromatography. The starting compounds for the preparation of the compounds of the formula (I) are commercially available or can be prepared according to or analogously to literature procedures. The compounds obtained with the above-mentioned synthesis methods are a further object of the present invention.

A part of the compounds falling under formula (I) are disclosed in the literature. However, their use as a pharmaceutical compound is not disclosed in any of these references. The compounds are for example disclosed in Tetrahedron.Lett. (1998), 39(29), 5195-5198; Tetrahedron.Lett. (1998), 39(5/6), 497-500; JP 0925552; WO 99/26927; WO 97/06158, US 5,583,221; WO 96/24588; Biorg.Med.Chem.Lett. (1996),6(8), 973-978; WO 95/30640;

EP-A 0 399 422; Helv. Chim. Acta (1977), 60(6), 2089-98; Ann. Chim. (Paris) (1976), 1(5), 269-76; Khim. Geterosikl.Soedin. (1974), (12), 1629-38; Chem:Ind (1974), (12), 495; Liebigs Ann. Chem. (1971), 743, 42-49; J. Org. Chem. (1970), 35(4), 1149-54; and ZA-A 6806875.

The present invention also relates to acylated indanyl amines according to the general formula (I) and their pharmaceutically acceptable salts for use as pharmaceuticals.



(I)

In the above formula (I),

R^1 and R^4 are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^9CO; $CONR^{10}R^{11}$; $COOR^{12}$; CF_3; halogenes; pseudohalogenes; $NR^{13}R^{14}$; OR^{15}; $S(O)_mR^{16}$; $SO_2NR^{17}R^{18}$; and NO_2;

R^2 and R^3 are independently from each other selected from the group consisting of: H; halogenes; pseudohalogenes; unsubstituted and at least monosubstituted C_1-C_6-alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_6-alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3; CN; NO_2; (C_1-C_6-alkyl)amino; di(C_1-C_6-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O-; unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and

piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1-C_3-alkyl, halogenes and methoxy;

A is CH_2, CHOH or CH-(C_1-C_3-alkyl);

B is CH_2 or CH-(C_1-C_3-alkyl);

R^5 is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogenes; pseudohalogenes; C_1-C_{10}-alkyl; C_3-C_5-alkandiyl; phenyl; phenylsubstituted C_1-C_4-alkyl; CF_3; OH; C_1-C_{10}-alkoxy; phenoxy; benzyloxy; CF_3O; (C_1-C_{10}-alkyl)COO; $S(O)_mR^{20}$; (C_1-C_{10}-alkyl)amino; di(C_1-C_{10}-alkyl)amino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_3-alkyl)-; (C_1-C_{10}-alkyl)-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; phenylamino; phenyl-CO; $COOR^{21}$; $CONR^{22}R^{23}$; $SO_2NR^{24}R^{25}$; and aromatic or aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, O and S which can be substituted by one ore more substituents from the group consisting of halogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; wherein all phenyl groups and phenyl-containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3;

R^6 is H, C_1-C_6-alkyl or benzyl;

R^7 is selected from the group consisting of:
H; C_1-C_6-alkyl which can be phenyl-substituted; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

R^8 is H or C_1-C_6-alkyl;

R^9 is C_1-C_6-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substitu ents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogenes, pseudohalogenes, and CF_3;

R^{10} independently has the same meaning as R^7;

R^{11} independently has the same meaning as R^8;

R^{12} independently has the same meaning as R^6;

R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{14} is H or C_1-C_6-alkyl;

R^{15} is selected from the group consisting of: H; C_1-C_6-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{16} is selected from the group consisting of: C_1-C_6-alkyl; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substitutents can be present;

R^{17} independently has the same meaning as R^7;

R^{18} independently has the same meaning as R^8;

R^{19} independently has the same meaning as R^{16};

R^{20} independently has the same meaning as R^{16};

R^{21} independently has the same meaning as R^6;

R^{22} independently has the same meaning as R^7;

R^{23} independently has the same meaning as R^8;

R^{24} independently has the same meaning as R^7;

R^{25} independently has the same meaning as R^8;

heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O and S;

aryl is phenyl, naphth-1-yl or naphth-2-yl;

m is 0, 1 or 2.

With respect to the definitions given above in the context of the compounds for use as pharmaceuticals according to the general formula (I), the same explanations as laid out above in the context with the compounds as such apply.

In preferred embodiments of the present invention, the substituents R^1 to R^5, A and B and the groups aryl and heteroaryl of the formula (I) independently from each other have the following meanings. Hence, one or more of the substituents R^1 to R^5 and A and B can have the preferred parcticularly preferred meanings specified below.

R^1 is preferably selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogenes; pseudohalogenes; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^1 is in particular halogene or C_1-C_4-alkyl.

R^2 is preferably selected from the group consisting of: H; halogenes; pseudohalogenes; and C_1-C_3-alkyl.

R^3 and R^4 are preferably each H;

A is preferably selected from the group consisting of CH_2 and CHOH; A is in particular CH.

B is preferably selected from the group consisting of CH_2 and CH-CH_3; B is particular CH_2.

R^5 is preferably selected from the group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_3-alkyl)amino, di(C_1-C_3-alkyl)amino, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -OCH_2-CH_2-O-; unsubstituted and at least mono-halogene-substituted benzodioxolyl and dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, –O-CH_2-O-, –O-CF_2-O-, and -O-CH_2-CH_2-O-; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -O-CH_2-CH_2-O-; R^5 is in particular selected from the group consisting of: 4-fluorophenyl; 4-chlorophenyl; 4-bromophenyl; 4-(C_1-C_3-alkyloxy)-phenyl; 4-trifluoromethoxyphenyl; 2-bromo-4-fluorophenyl; 2-chloro-4-fluorophenyl; 3,4-dimethylphenyl; 2,4-dimethylphenyl; 4-chloro-2-methylphenyl; 2-hydroxy-4-methylphenyl; 2-hydroxy-4-ethoxyphenyl; 2-methoxy-4-methylphenyl; 4-phenoxyphenyl; 3-fluoro-4-methylphenyl; benzo[1,3]dioxol-5-yl; 2,2-difluoro-benzo[1,3]dioxol-5-yl; 2,3-dihydrobenzofuran-5-yl; thienyl; halogene-substituted thienyl; 5-acetylthienyl; pyridyl; halogene-substituted pyridyl; and (C_1-C_3-alkyl)-substituted pyridyl.

Heteroaryl is preferably selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms from the group consisting of N, O, and S; heteroaryl is in particular selected from the group consisting of furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

Aryl is preferably phenyl;

m is preferably 0 or 2.

Compounds of the formula (I) for use as pharmaceutical, in which all of the above-mentioned groups have the preferred meanings or the particularly preferred meanings defined above are also an object of the present invention.

The compounds according to the general formula (I) can be used to upregulate the expression of the endothelial NO synthase and are helpful pharmaceutical compounds for the treatment of various diseases. In the context of the present invention, treatment includes the therapy as well as the prophylaxis of the respective diseases.

Examples of diseases which can be treated with the compounds according to the present invention include cardiovascular diseases like stable and unstable angina pectoris, coronary heart disease, Prinzmetal angina (spasm), acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease (PAOD), endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension including essential hypertension, pulmonary hypertension, and secondary hypertension (renovascular hypertension, chronic glomerulonephritis), erectile dysfunction, ventricular arrhythmia, and the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptiva.

Compounds of the formula (I) can additionally be used in the therapy and prophylaxis of diabetes and diabetes complications (nephropathy, retinopathy), angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, restricted memory performance or a restricted ability to learn.

Preferred indications are stable angina pectoris, coronary heart disease, hypertension, endothelial dysfunction, atherosclerosis and diabetes complications.

The compounds according to the formula (I) can also be used in combination with other pharmaceutically active compounds, preferably compounds which are able to enhance the effect of the compounds according to the general formula (I). Examples of such compounds include:
statins; ACE-inhibitors; AT1-antagonists; argininase-inhibitors; PDE V-inhibitors; Ca-antagonists; alpha-blockers; beta-blockers; metimazol and analogous compounds; arginine; tetrahydrobiopterin; vitamins, in particular vitamin C and vitamin B6; niacine.

The compounds of the formula (I) and their pharmaceutically acceptable salts, optionally in combination with other pharmaceutically active compounds, can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of pharmaceutical preparations. Further subjects of the present invention therefore also are the compounds of the formula (I) and their pharmaceutically acceptable salts for use as pharmaceuticals, their use as

transcription stimulating agent for endothelial NO synthase and in particular their use in the therapy and prophylaxis of the above-mentioned syndromes as well as their use for preparing medicaments for these purposes. Furthermore, subjects of the present invention are pharmaceutical preparations (or pharmaceutical compositions) which comprise an effective dose of at least one compound of the formula (I) and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, i.e. one or more pharmaceutically acceptable carrier substances and/or additives.

The pharmaceuticals according to the invention can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of solutions for injection or infusion. Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or the inhalative administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the disease to be treated and on its severity.

The amount of compounds of the formula (I) and/or its pharmaceutically acceptable salts in the pharmaceutical preparations normally ranges from 0.2 to 800 mg, preferably from 0.5 to 500 mg, in particular from 1 to 200 mg, per dose, but depending on the type of the pharmaceutical preparation it may also be higher. The pharmaceutical preparations usually comprise 0.5 to 90 percent by weight of the compounds of the formula (I) and/or their pharmaceutically acceptable salts. The preparation of the pharmaceutical preparations can be carried out in a manner known per se. To this end, one or more compounds of the formula (I) and/or their pharmaceutically acceptable salts, together with one or more solid or liquid pharmaceutical carrier substances and/or additives (or auxiliary substances) and, if desired, in combination with other pharmaceutically active compounds having therapeutic or prophylactic action, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human or veterinary medicine.

For the production of pills, tablets, sugar-coated tablets and hard gelatin capsules it is possible to use, for example, lactose, starch, for example maize starch, or starch derivatives, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or

hardened oils, etc. Suitable carriers for the preparation of solutions, for example of solutions for injection, or of emulsions or syrups are, for example, water, physiologically sodium chloride solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils, etc. It is also possible to lyophilize the compounds of the formula (I) and their pharmaceutically acceptable salts and to use the resulting lyophilisates, for example, for preparing preparations for injection or infusion. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

Besides the compound or compounds according to the invention and carriers, the pharmaceutical preparations can also contain additives, for example fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dosage of the compound of the formula (I) to be administered and/or of a pharmaceutically acceptable salt thereof depends on the individual case and is, as is customary, to be adapted to the individual circumstances to achieve an optimum effect. Thus, it depends on the nature and the severity of the disorder to be treated, and also on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the efficacy and duration of action of the compounds used, on whether the therapy is acute or chronic or prophylactic, or on whether other active compounds are administered in addition to compounds of the formula (I). In general, a daily dose of approximately 0.01 to 100 mg/kg, preferably 0.1 to 10 mg/kg, in particular 0.3 to 5 mg/kg (in each case mg per kg of bodyweight) is appropriate for administration to an adult weighing approximately 75 kg in order to obtain the desired results. The daily dose can be administered in a single dose or, in particular when larger amounts are administered, be divided into several, for example two, three or four individual doses. In some cases, depending on the individual response, it may be necessary to deviate upwards or downwards from the given daily dose.

The compounds according to the formula (I) can also be used for other purposes than those indicated in the foregoing. Non-limiting examples include diagnostic purposes, the use as biochemical tools, and as intermediates for the preparation of further compounds, e.g. pharmaceutically active compounds.

The present invention will now be illustrated in the following examples:

Examples:

EX 1: 4-FLUORO-N-(4-METHYL-INDAN-2-YL)-BENZAMIDE

370mg (2.52mmol) 2-amino-4-methylindane and 257mg (2.52mmol) triethylamine were dissolved in 5 ml dioxane, 400mg (2.52 mmol) 4-fluorobenzoylchloride were added, and the mixture was stirred for 2 h at RT.

The resulting mixture was then poured onto an ice/HCl-mixture, extracted with ethyl acetate and concentrated. The thus-obtained residue was fractionated with prep. HPLC (RP18, acetonitrile/water, 0.1% trifluoroacetic acid). Yield: 370 mg (87%), mp.:154°C

^{1}H (d6-DMSO, 300MHz): 2.20 (s, 3H, CH_3), 2.80-3.00 (m, 2H, -CH_2-), 3.16-3.30 (m, 2H, -CH_2-), 4.69 (quint, 1H, CH-N), 6.92-7.10 (m, 3H, H^5, H^6, H^7), 7.39 (t, 2H, $H^{3'}$, $H^{5'}$), 7.94 (dd, 2H, $H^{2'}$, $H^{6'}$), 8.67 (d, 1H, NH)

The enantiomers were separated by prep. HPLC (Chiralpeak AD, elution agent n-heptane:isopropanol 10:1):,

a) (-)-4-Fluoro-N-(4-methyl-indan-2-yl)-benzamide

R_f-value: 8.69

b) (+)-4-Fluoro-N-(4-methyl-indan-2-yl)-benzamide

R_f-value: 9.46

The following compounds were obtained in an analogous way:

EX 2: 4-FLUORO-N-(5-METHOXY-INDAN-2-YL)-BENZAMIDE

mp.: 160°C

EX 3: 4-FLUORO-N-(5,6-DIMETHOXY-INDAN-2-YL)-BENZAMIDE

mp.: 160°C

EX 4: 4-FLUORO-N-(5-FLUORO-INDAN-2-YL)-BENZAMIDE

mp.: 144°C

EX 5: 4-FLUORO-N-(5-METHYL-INDAN-2-YL)-BENZAMIDE
mp.: 143°C

EX 6: ACETIC ACID 5-ETHOXY-2-(INDAN-2-YLCARBAMOYL)-PHENYL ESTER
mp.: 139°C

EX 7: ACETIC ACID 2-(INDAN-2-YLCARBAMOYL)-5-METHYL-PHENYL ESTER
mp.: 116°C

EX 8: 4-FLUORO-N-(TRANS-1-HYDROXY-INDAN-2-YL)-BENZAMIDE
mp.: 247°C

EX 9: BENZO[1,3]DIOXOL-5-CARBOXYLICACID (5-NITRO-INDAN-2-YL)-AMIDE
mp: 229°C

EX 10: BENZO[1,3]DIOXOL-5-CARBOXYLICACID (6-CHLOR-1-HYDROXY-INDAN-2-YL)-AMIDE
mp: 255°C

EX 11: 4-FLUORO-N-(4-FLUORO-INDAN-2-YL)-BENZAMIDE
[M+H+] measured: 274
R_f-value: 4,91

EX 12: 4-FLUORO-N-(4-HYDROXY-INDAN-2-YL)-BENZAMIDE
[M+H+] measured: 272
R_f-value: 4,37

EX 13: 4-FLUORO-N-(4-ISOPROPOXY-INDAN-2-YL)-BENZAMIDE
[M+H+] measured: 314
R_f-value: 5,21

EX 14: N-(5,6-DICHLORO-INDAN-2-YL)-4-FLUORO-BENZAMIDE
[M+H+] measured: 324

R_f-value: 5,01

EX 15A: N-(4-CHLORO-INDAN-2-YL)-4-FLUORO-BENZAMIDE

[M+H+] measured: 290

R_f-value: 4,94 (Rf on prep. HPLC (Chiralpeak AD, solvent acetonitril:isopropanol 9:1))

EX 15B: N-(4-CHLORO-INDAN-2-YL)-4-FLUORO-BENZAMIDE

[M+H+] measured: 290

R_f-value: 16,79 (Rf on prep. HPLC (Chiralpeak AD, solvent acetonitrile:isopropanol 9:1))

One of the compounds of examples 15A and 15B is the R enantiomer and the other one is the S enantiomer.

EX 16A: N-(5-CHLORO-INDAN-2-YL)-4-FLUORO-BENZAMIDE

[M+H+] measured: 290

R_f-value: 7,21 (Rf on prep. HPLC (Chiralpeak AD, solvent acetonitrile:isopropanol 9:1))

EX 16B: N-(5-CHLORO-INDAN-2-YL)-4-FLUORO-BENZAMIDE

[M+H+] measured: 290

R_f-value: 20,12 (Rf on prep. HPLC (Chiralpeak AD, solvent acetonitrile:isopropanol 9:1))

One of the compounds of examples 16A and 16B is the R enantiomer and the other one is the S enantiomer.

EX 17: N-(4,7-DIMETHOXY-INDAN-2-YL)-4-FLUORO-BENZAMIDE

[M+H+] measured: 316

R_f-value: 4,81

EX 18: 4-FLUORO-N-(INDAN-2-YL)-BENZAMIDE

43.70g (258mol) 2-aminoindane hydrochloride and 53.43g (528mmol) triethylamine were added to 250 ml of tetrahydrofuran, 42.89g (270 mmol) 4-fluorobenzoylchloride were added, and the mixture was stirred for 2 h at RT.

The resulting mixture was then poured onto an ice/HCl-mixture, the obtained precipitate was filtered, washed with a $NaHCO_3$-solution and water and dried in vacuo. The crude product was crystallized from methanol. There were obtained 47.8 g (73%) of a white, crystalline product.

mp.:167°C

MS: $M+H^+$:256.1

^{1}H-NMR (300 MHz, d_6-DMSO): 2.96 (dd, 2H, H1/3), 3.25 (dd, 2H, H3/1), 4.70 (sextett, 1H, H2), 7.12 - 7.19 (m, 2H, H4,7/5,6), 7.20 - 7.28 (m, 2H, H5,6/4,7), 7.30 (t, 2H, H3', 5'), 7.95 (dd, 2H, H2',6'), 8.68 (d, 1H, NH)

COUPLING OF INDANYL AMINES WITH VARIOUS AROMATIC CARBOXYLIC ACIDS

Method A:

0.5 mmol (96mg) 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride and 0.5 mmol (87µl) DIPEA were dissolved in 2.5ml of dichloromethane, added to a solution of 0.5mmol of the respective acid in 2.5ml of DCM and stirred for 10 min at RT. There were then added 0.7mmol (93mg) 2-aminoindane, and stirring was continued over night.

The resulting solution was then washed 2 x with 2N HCl and once with a saturated $KHCO_3$-solution, dried over $MgSO_4$, filtered and the residue obtained after evaporating to dryness was crystallized from ethyl acetate/hexane- or MeOH-diethylether-mixtures or purified with HPLC.

The retention times given are those obtained on a Beckmann HPLC-system using a YMC ODS-AM 4.6x250mm-column and acetonitrile/water/0,1%TFA-gradient (0% acetonitrile to 80% acetonitrile in 40 min) under a flow of 1 ml/min.

EX 19: 2-HYDROXY-N-INDAN-2-YL-4-METHYL-BENZAMIDE

mp.: 163°C

EX 20: 4-ETHOXY-2-HYDROXY-N-INDAN-2-YL-BENZAMIDE

mp.: 163°C

EX 21: 3-FLUORO-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 256.2

R_f-value: 15.48

EX 22: 3-ETHOXY-4-METHOXY-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 312.2
R_f-value: 15.38

EX 23: 4-ETHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 282.2
R_f-value: 16.62

EX 24: 4-CHLORO-3-METHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 286.2
R_f-value: 17.60

EX 25: 4-ISOPROPYLOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 296.2
R_f-value: 17.96

EX 26: 3,4-DIMETHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 266.2
R_f-value: 17.71

EX 27: 4-BUTOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 310.2
R_f-value: 20.83

EX 28: 3-CHLORO-4-METHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 302.2
R_f-value: 17.27

EX 29: 4-PHENOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 330.2
R_f-value: 20.54

EX 30: 3-BROMO-4-FLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 334.2
R_f-value: 18.71

EX 31: 3-CHLORO-4-METHYL-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 286.2
R_f-value: 19.23

EX 32: 3-FLUORO-4-METHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 286.2
R_f-value: 15.75

EX 33: 3,4-DIMETHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 298.2
R_f-value: 13.93

EX 34: 3-CHLORO-4-FLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 290.2
R_f-value: 18.26

EX 35: 2,4-DIMETHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 266.2
R_f-value: 16.84

EX 36: 3,4-DIFLUOR-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 274.2
R_f-value: 16.47

EX 37: 4-BENZYLOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 344.2
R_f-value: 20.38

EX 38: 5-BROMO-THIOPHEN-2-CARBOXYLIC ACID- INDAN-2-YLAMIDE
[M+H+] measured: 322.2
Rf-value: 18.14

EX 39: 3-BENZYLOXY-4-METHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 374.2
R_f-value: 19.62

EX 40: 4-FLUORO-NAPHTHALENE-1-CARBOXYLIC ACID- INDAN-2-YLAMIDE

[M+H+] measured: 306.2

R_f-value: 18.47

EX 41: 5-CHLORO-THIOPHEN-2-CARBOXYLIC ACID- INDAN-2-YLAMIDE

[M+H+] measured: 278.2

R_f-value: 17.74

EX 42: 4-CHLORO-3-METHYL-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 286.2

R_f-value: 19.14

EX 43: 4-CHLORO-3-METHOXY-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 302.2

R_f-value: 18.42

EX 44: 3-METHOXY-4-METHYL-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 282.2

R_f-value: 18.20

EX 45: 2-CHLORO-4,5-DIMETHOXY-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 332.2

R_f-value: 15.27

EX 46: 2-METHOXY-4-METHYL-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 282.2

R_f-value: 18.10

EX 47: 4-TRIFLUOROMETHYLOXY-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 322.2

R_f-value: 19.90

EX 48: 3-FLUORO-4-METHYL-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 270.2

R_f-value: 18.09

EX 49: 4-METHOXY-3-METHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 282.2
R_f-value: 17.73

EX 50: 4-PROPYLOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 296.2
R_f-value: 19.60

EX 51: 3,4-DIETHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 326.2
R_f-value: 17.67

EX 52: 4-(CYCLOHEX-2-ENYLOXY)-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 334.2
R_f-value: 21.53

EX 53: 2,3-DIHYDRO-BENZOFURAN-5-CARBONSAEURE INDAN-2-YLAMIDE
[M+H+] measured: 280.2
R_f-value: 15.67

EX 54: 4-FLUORO-2-TRIFLUORMETHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 324.2
R_f-value: 16.54

EX 55: 3-FLUORO-2-METHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 270.2
R_f-value: 16.54

EX 56: 4-FLUORO-3-METHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 286.2
R_f-value: 16.65

EX 57: 3,5-DIFLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 274.2
R_f-value: 17.76

EX 58: 2-BROMO-4-FLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 334.2
R_f-value: 16.73

EX 59: 4-FLUORO-3-TRIFLUORMOETHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 324.2
R_f-value: 20.31

EX 60: 5-ACETYL-THIOPHEN-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 286.2
R_f-value: 14.20

EX 61: 5-METHYL-THIOPHEN-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 258.2
R_f-value: 15.67

EX 62: 2-CHLORO-4-FLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 290.2
R_f-value: 15.70

EX 63: 2,2-DIFLUORO-BENZO[1,3]DIOXOL-5-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 318.2
R_f-value: 18.73

EX 64: 2-PHENOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 330.2
R_f-value: 20.77

EX 65: 2,4-DIFLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 274.2
R_f-value: 15.93

EX 66: 4-CHLORO-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 272.2
R_f-value: 17.00

EX 67: 4-CHLORO-2-HYDROXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 288.2
R_f-value: 20.87

EX 68: 2-HYDROXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 254.1
R_f-value: 17.15

EX 69: N,N'-DI-INDAN-2-YL-PHTHALAMIDE
[M+H+] measured: 397.2
R_f-value: 16.89

EX 70: 2-AMINO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 253.1
R_f-value: 19.26

EX 71: 2-(INDAN-2-YLAMINOCARBONYL)-BENZOIC ACID
[M+H+] measured: 282.2
R_f-value: 18.48

EX 72: 2-ACETYLAMINO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 295.2
R_f-value: 13.39

EX 73: BENZO[1,3]DIOXOL-5-CARBOXYLIC ACID INDAN-2-YL AMIDE
mp.: 175,4 °C

Method B:
To 0.75 mmol of the corresponding acid and 271 µl (1.575 mmole) diisopropylethylamine (DIPEA) in 5 ml tetrahydrofuran were given 271 mg (0.825 mmol) TOTU (dissolved in 1 ml DMF) After 15 min stirring at room temperature a mixture of 153 mg (0.900 mmol) 2-aminoindan hydrochloride and 172 µl (1.000 mmol) DIPEA in 1 ml DMF was added. After stirring for 6h the mixture was filtered and evaporated. The residue was taken up in

ethyl acetate and washed successively with 20 ml 1n HCL and 20 ml 5% sodium hydrogencarbonate solution. The resulting organic phase was evaporated and purified via prep. HPL C. (RP 18, Acetonitril/Water).

The retention times given were obtained on a HPLC-MS-System (HP 1100, Detector: HP DAD G1315A) using a Merck Lichro CART 55-2 Purosphere STAR RP 18e 3µ, an acetonitril/water+0.1% formic acid (B) gradient (95%B to 5% B in 1,25 min, 5%B for 3,5 min, 5% B bis 95%B in 0,25 min, and 95%B für 0,5 min under a flow of of 0,75 ml/min

EX 74: 2,5-DIFLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 274
R_f-value: 3,13

EX 75: 2,6-DIFLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 274
R_f-value: 3,09

EX 76: 2-CHLORO-6-FLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 290
R_f-value: 3,18

EX 77: N-INDAN-2-YL-2-PHENYLAMINO-BENZAMIDE
[M+H+] measured: 329
R_f-value: 3,45

EX 78: N-INDAN-2-YL-2,3-DIMETHOXY-BENZAMIDE
[M+H+] measured: 298
R_f-value: 3,17

EX 79: N-INDAN-2-YL-2,3,4-TRIMETHOXY-BENZAMIDE
[M+H+] measured: 328
R_f-value: 3,32

EX 80: N-INDAN-2-YL-2,4-DIMETHOXY-BENZAMIDE
[M+H+] measured: 298
R_f-value: 3,17

EX 81: N-INDAN-2-YL-2,6-DIMETHOXY-BENZAMIDE
[M+H+] measured: 298
R_f-value: 3,01

EX 82: 2-ETHOXY-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 282
R_f-value: 3,31

EX 83: BIPHENYL-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 314
R_f-value: 3,24

EX 84: N-INDAN-2-YL-PHTHALAMIC ACID METHYL ESTER
[M+H+] measured: 296
R_f-value: 3,01

EX 85: 2-(4-FLUORO-BENZOYL)-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 360
R_f-value: 3,29

EX 86: 2-ACETYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 280
R_f-value: 3,10

EX 87: N-INDAN-2-YL-2,3-DIMETHYL-BENZAMIDE
[M+H+] measured: 266
R_f-value: 3,18

EX 88: N-INDAN-2-YL-2,6-DIMETHYL-BENZAMIDE
[M+H+] measured: 266
R_f-value: 3,20

EX 89: 2-BENZYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 328
R_f-value: 3,28

EX 90: N-INDAN-2-YL-2-(2-PHENETHYL)-BENZAMIDE

[M+H+] measured: 342
R_f-value: 3,36

EX 91: 3-BROMO-N-INDAN-2-YL-4-METHYL-BENZAMIDE
[M+H+] measured: 331
R_f-value: 3,32

EX 92: N-INDAN-2-YL-3,4,5-TRIMETHOXY-BENZAMIDE
[M+H+] measured: 328
R_f-value: 3,10

EX 93: N-INDAN-2-YL-3-TRIFLUOROMETHYL-BENZAMIDE
[M+H+] measured: 306
R_f-value: 3,27

EX 94: 4-CYANO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 263
R_f-value: 3,06

EX 95: 4-ACETYLAMINO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 295
R_f-value: 2,88

EX 96: 4-ETHYLSULFANYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 298
R_f-value: 3,25

EX 97: N-INDAN-2-YL-TEREPHTHALAMIC ACID METHYL ESTER
[M+H+] measured: 296
R_f-value: 3,12

EX 98: 4-BENZOYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 342
R_f-value: 3,25

EX 99: 4-ACETYL-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 280
R_f-value: 3,02

EX 100: 5-FLUORO-1H-INDOLE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 295
R_f-value: 3,14

EX 101: 1H-INDOLE-3-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 277
R_f-value: 3,06

EX 102: 1H-INDOLE-5-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 277
R_f-value: 3,05

EX 103: 1-METHYL-1H-INDOLE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 291
R_f-value: 3,29

EX 104: PYRAZINE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 240
R_f-value: 2,92

EX 105: 2-CHLORO-N-INDAN-2-YL-NICOTINAMIDE
[M+H+] MEASURED: 273
R_f-value: 2,95

EX 106: 2-HYDROXY-N-INDAN-2-YL-6-METHYL-NICOTINAMIDE
[M+H+] measured: 269
R_f-value: 2,86

EX 107: PYRIDINE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 239
R_f-value: 3,14

EX 108: 5-BUTYL-PYRIDINE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 295
R_f-value: 3,49

EX 109: 2-PHENYL-QUINOLINE-4-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 365
R_f-value: 3,40

EX 110: QUINOLINE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 289
R_f-value: 3,30

EX 111: QUINOLINE-4-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 289
R_f-value: 2,98

EX 112: N-INDAN-2-YL-4-METHANESULFONYL-BENZAMIDE
[M+H+] measured: 316
R_f-value: 2,99

EX 113: N-INDAN-2-YL-4-SULFAMOYL-BENZAMIDE
[M+H+] measured: 317
R_f-value: 2,98

EX 114: 2-HYDROXY-N-INDAN-2-YL-NICOTINAMIDE
[M+H+] measured: 255
R_f-value: 2,80

EX 115: N-INDAN-2-YL-2-METHOXY-4-METHYLSULFANYL-BENZAMIDE
[M+H+] measured: 314
R_f-value: 3,33

EX 116: 1H-BENZIMIDAZOLE-5-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 278
R_f-value: 2,51

EX 117: 1H-BENZOTRIAZOLE-5-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 279
R_f-value: 2,89

EX 118: 2,4,5-TRIFLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 292
R_f-value: 3,21

EX 119: N-INDAN-2-YL-N'-(CS)-1-PHENYL-ETHYL)-PHTHALAMIDE
[M+H+] measured: 385
R_f-value: 3,13

EX 120: N-INDAN-2-YL-2-(4-METHYL-BENZOYL)-BENZAMIDE
[M+H+] measured: 356
R_f-value: 3,29

EX 121: 3-(2-CHLORO-PHENYL)-5-METHYL-ISOXAZOLE-4-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 353
R_f-value: 3,16

EX 122: 4-ACETYL-3,5-DIMETHYL-1H-PYRROLE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 297
R_f-value: 2,93

EX 123: 4-CYCLOHEXYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 320
R_f-value: 3,48

EX 124: 4-BROMO-N-INDAN-2-YL-2-METHYL-BENZAMIDE
[M+H+] measured: 330
R_f-value: 3,21

EX 125: N-INDAN-2-YL-3-TRIFLUOROMETHOXY-BENZAMIDE
[M+H+] measured: 322
R_f-value: 3,23

EX 126: 2,4,6-TRIFLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 292
R_f-value: 3,01

EX 127: 4-CHLORO-2-FLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 290
R_f-value: 3,21

EX 128: N-INDAN-2-YL-PHTHALAMIC ACID TERT-BUTYL ESTER
[M+H+] measured: 281 (-tert.- butyl)
R_f-value: 3,14

EX 129: 3-CHLORO-THIOPHENE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 278
R_f-value: 3,25

EX 130: N-INDAN-2-YL-2-PYRROL-1-YL-BENZAMIDE
[M+H+] measured: 303
R_f-value: 3,18

EX 131: 5-METHYL-2-PHENYL-2H-[1,2,3]TRIAZOLE-4-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 319
R_f-value: 3,42

EX 132: 3,5-DIMETHYL-ISOXAZOLE-4-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 257
R_f-value: 2,98

EX 133: 2-ETHYLSULFANYL-N-INDAN-2-YL-NICOTINAMIDE
[M+H+] measured: 299
R_f-value: 3,11

EX 134: 2-(2,3-DIMETHYL-PHENYLAMINO)-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 357
R_f-value: 3,68

EX 135: 4-DIMETHYLAMINO-NAPHTHALENE-1-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 331
R_f-value: 3,20

EX 136: 2-ACETYLAMINO-6-CHLORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 329
R_f-value: 2,97

EX 137: 2-CHLORO-N-INDAN-2-YL-6-METHYL-ISONICOTINAMIDE
[M+H+] measured: 287
R_f-value: 3,11

EX 138: 5-CHLORO-6-HYDROXY-N-INDAN-2-YL-NICOTINAMIDE
[M+H+] measured: 289
R_f-value: 2,80

EX 139: 7-METHOXY-BENZOFURAN-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 308
R_f-value: 3,20

EX 140: 2-FLUORO-N-INDAN-2-YL-5-TRIFLUOROMETHYL-BENZAMIDE
[M+H+] measured: 324
R_f-value: 3,29

EX 141: 5-METHYL-1-PHENYL-1H-PYRAZOLE-4-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 318
R_f-value: 3,14

EX 142: 5-METHYL-PYRAZINE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 254
R_f-value: 2,97

EX 143: 2-(2-CYANO-PHENYLSULFANYL)-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 371
R_f-value: 3,23

EX 144: N-INDAN-2-YL-2,6-DIMETHOXY-NICOTINAMIDE
[M+H+] measured: 299
R_f-value: 3,23

EX 145: 2-CHLORO-4,5-DIFLUORO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 308
R_f-value: 3,20

EX 146: N-INDAN-2-YL-4-PYRROL-1-YL-BENZAMIDE
[M+H+] measured: 303
R_f-value: 3,20

EX 147: 3,5-DI-TERT-BUTYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 351
R_f-value: 3,62

EX 148: 2-CHLORO-N-INDAN-2-YL-6-METHYL-NICOTINAMIDE
[M+H+] measured: 287
R_f-value: 3,01

EX 149: 3-BENZOYL-PYRIDINE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 343

R_f-value: 3,21

EX 150: 1H-INDOLE-6-CARBOXYLIC ACID INDAN-2-YLAMIDE

[M+H+] measured: 277

R_f-value: 3,00

EX 151: 1H-INDAZOLE-3-CARBOXYLIC ACID INDAN-2-YLAMIDE

[M+H+] measured: 278

R_f-value: 3,02

EX 152: 5-(4-CHLORO-PHENYL)-FURAN-2-CARBOXYLIC ACID INDAN-2-YLAMIDE

[M+H+] measured: 338

R_f-value: 3,40

EX 153: 2,6-DICHLORO-N-INDAN-2-YL-ISONICOTINAMIDE

[M+H+] measured: 307

R_f-value: 3,22

EX 154: N-INDAN-2-YL-4-METHYLAMINO-BENZAMIDE

[M+H+] measured: 267

R_f-value: 3,55

EX 155: 4-BUTYLAMINO-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 309

R_f-value: 6,06

EX 156: 4-DIMETHYLAMINO-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 281

R_f-value: 5,44

EX 157: BIPHENYL-4-CARBOXYLIC ACID INDAN-2-YLAMIDE

[M+H+] measured: 314

R_f-value: 3,94

EX 158: N-INDAN-2-YL-4-TRIFLUOROMETHYL-BENZAMIDE

[M+H+] measured: 306
R_f-value: 3,36

EX 159: 4-ETHYL-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 266
R_f-value: 3,19

EX 160: 1-METHYL-1H-PYRROLE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 241
R_f-value: 3,00

EX 161: 5-BROMO-FURAN-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 306
R_f-value: 3,08

EX 162: 2-ETHOXY-NAPHTHALENE-1-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 332
R_f-value: 3,19

EX 163: 1H-PYRROLE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 227
R_f-value: 2,88

EX 164: 3-METHYL-THIOPHENE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 258
R_f-value: 3,08

EX 165: THIOPHENE-3-CARBOXYLIC ACID INDAN-2-YLAMIDE
[M+H+] measured: 244
R_f-value: 2,96

EX 166: N-INDAN-2-YL-1-OXY-ISONICOTINAMIDE
[M+H+] measured: 255
R_f-value: 2,51

EX 167: 6-HYDROXY-N-INDAN-2-YL-NICOTINAMIDE
[M+H+] measured: 255
R_f-value: 2,60

EX 168: 2-AMINO-N-INDAN-2-YL-NICOTINAMIDE
[M+H+] measured: 254
R_f-value: 1,55

EX 169: 6-AMINO-N-INDAN-2-YL-NICOTINAMIDE
[M+H+] measured: 254
R_f-value: 1,62

EX 170: N-INDAN-2-YL-6-METHYL-NICOTINAMIDE
[M+H+] measured: 253
R_f-value: 2,43

EX 171: N-INDAN-2-YL-NICOTINAMIDE
[M+H+] measured: 239
R_f-value: 2,63

EX 172: N-INDAN-2-YL-ISONICOTINAMIDE
[M+H+] measured: 239
R_f-value: 2,56

EX 173: N-INDAN-2-YL-2-METHYL-NICOTINAMIDE
[M+H+] measured: 253
R_f-value: 1,59

EX 174: 3-ACETYLAMINO-N-INDAN-2-YL-BENZAMIDE
[M+H+] measured: 295
R_f-value: 2,83

EX 175: N-INDAN-2-YL-4-PENTYLOXY-BENZAMIDE
[M+H+] measured: 324

R_f-value: 3,41

EX 176: N-INDAN-2-YL-4-PROPYL-BENZAMIDE

[M+H+] measured: 280

R_f-value: 3,28

EX 177: 3-CHLORO-BENZO[B]THIOPHENE-2-CARBOXYLIC ACID INDAN-2-YLAMIDE

[M+H+] measured: 328

R_f-value: 3,44

EX 178: N-INDAN-2-YL-2-PHENOXY-NICOTINAMIDE

[M+H+] measured: 331

R_f-value: 3,20

EX 179: 2-DIMETHYLAMINO-N-INDAN-2-YL-BENZAMIDE

[M+H+] measured: 281

R_f-value: 2,86

EX 180: N-INDAN-2-YL-2,4,6-TRIMETHOXY-BENZAMIDE

[M+H+] measured: 328

R_f-value: 2,98

EX 181: N-INDAN-2-YL-4-(2,2,2-TRIFLUORO-1,1-DIHYDROXY-ETHYL)-BENZAMIDE

[M+H+] measured: 352

R_f-value: 3,01

EX 182: 4-FLUORO-N-(5-NITRO-INDAN-2-YL)-BENZAMIDE

To 5.0g (19.6mmol) 4-Fluoro-N-(indan-2-yl)-benzamide is given, at 5-10°C, a nitrating mixture of 10ml conc. nitric acid and 12 ml conc. sulfuric acid, followed by stirring over 3 h at RT. The mixture was worked up by pouring onto an ice/water mixture, extraction with ethyl acetate, washing of the organic phase with a solution of sodium hydrogencarbonate, drying and evaporating to dryness. The thus-obtained residue was crystallized form ethyl acetate/heptane. yield: 3.2g (54%), mp.: 167°C

EX 183: N-(5-AMINO-INDAN-2-YL)-4-FLUOROBENZAMIDE

1.20g (4.0mmol) 4-Fluoro-N-(5-nitro-indan-2-yl)-benzamide were hydrogenated in 100ml of ethanol on a Pd/carbon catalyst at RT.

After the removal of the catalyst, 955mg (ca.88%) product were obtained, which were used in the further reaction steps without any further purification.

EX 184: N-(5-BENZOYLAMINO-INDAN-2-YL)-4-FLUOROBENZAMIDE

100mg (0.37mmol) N-(5-Amino-indan-2-yl)-4-fluorobenzamide and 41.2mg (0.41mmol) triethylamine were dissolved in 2.5 ml THF, 57.2mg (0.41mmol) benzoyl chloride were added, and the whole was stirred over 6h at RT. The mixture was then poured onto an ice/HCl mixture, the precipitate was filtered off and purified by prep. HPLC (RP18, acetonitrile/water, 1% trifluoroacetic acid).yield: 80 mg (58%)

[M+H+] measured: 375.1

R_f-value: 4.92 (95% H_2O (0,05%TFA) to 95% acetonitrile, 4min, 95% acetonitrile 1,5min, Merck Porospher 3µ, 2x55mm)

There were obtained in an analogous way:

EX 185: N-(5-ACETYLAMINO-INDAN-2-YL)-4-FLUOROBENZAMIDE

[M+H+] measured: 313.1

R_f-value: 4.30 (95% H_2O (0,05%TFA) to 95% acetonitrile, 4min, 95% acetonitrile 1.5min, Merck Porospher 3µ, 2x55mm)

EX 186: 4-FLUORO-N-(5-(2-METHYLPROPIONYLAMINO)-INDAN-2-YL)BENZAMIDE

[M+H+] measured: 341.1

R_f-value: 4.68 (95% H_2O (0,05%TFA) to 95% acetonitrile, 4min, 95% acetonitrile 1.5min, Merck Porospher 3µ, 2x55mm)

EX 187: 4-FLUORO-N-(5-METHANSULFONYLAMINO-INDAN-2-YL)BENZAMIDE

[M+H+] measured: 349.2

R_f-value: 4.47 (95% H_2O (0.05%TFA) to 95% acetonitrile, 4min, 95% acetonitrile 1.5min, Merck Porospher 3µ, 2x55mm)

EX 188: N-(5-BENZOLSUFONYLAMINO-INDAN-2-YL)-4-FLUOROBENZAMIDE

[M+H+] measured: 411.2

R_f-value: 4.89 (95% H_20 (0.05%TFA) to 95% acetonitrile, 4min, 95% acetonitrile 1.5min, Merck Porospher 3µ, 2x55mm)

EX 189: N-(4-BROMOINDAN-2-YL)-4-FLUORO-BENZAMIDE AND N-(5-BROMO-INDAN-2-YL)-4-FLUORO-BENZAMIDE

8.0g (31.3mmol) N-(indan-2-yl)-4-fluoro-benzamide were dissolved in 125 ml DMF, 926 mg (3.1mmol) Fe(III)-chloride were added, then 5.26g (32,9mmol) bromine were added dropwise. After 3d stirring at RT the mixture was poured onto ice and extracted with ethyl acetate. After drying and evaporation, 6.2 g of a crystalline product were obtained.

The two isomers were obtained from this mixture by means of a prep. HPLC-separation (silica, heptane/ethyl acetate).

EX 189A N-(4-BROMOINDAN-2-YL)-4-FLUORO-BENZAMIDE

mp.: 169°C

EX 189B: N-(5-BROMO-INDAN-2-YL)-4-FLUORO-BENZAMIDE

mp.: 140°C

EX 190A: 4-FLUORO-N-[5-(4-FLUOROPHENYL)-INDAN-2-YL]-BENZAMIDE

251mg (1.8mmol) 4-fluorobenzene boronic acid, 500 mg (1.5mmol) of a mixture of N-(4-bromo-indan-2-yl)-4-fluoro-benzamide (relative amount 20%) and N-(5-bromo-indan-2-yl)-4-fluoro-benzamide (relative amount 80%) , 708mg (2.24mmol) barium hydroxide octahydrate and 50 mg tetrakis(triphenylphosphine)-palladium were suspended in 10ml of water and 10ml of dimethoxyethane, under an argon atmosphere, and stirred over 2h at 80°C. The mixture was poured onto ice water, the formed precipitate was filtered off and crystallized from ethyl acetate/hexane. 170 mg (27%) 4-fluoro-N-[5-(4-fluorophenyl)-indan-2-yl]-benzamide, mp.: 193°C, were obtained.

EX 190B: 4-FLUORO-N-[4-(4-FLUOROPHENYL)-INDAN-2-YL]-BENZAMIDE

From the mother liquor of Ex 190A, there were obtained, by prep. HPLC, (RP18, acetonitrile/water,1% trifluoroacetic acid) 71mg (11%) 4-fluoro-N-[4-(4-fluorophenyl)-indan-2-yl]-benzamide, mp.: 157°C.

EX 191: N-(5-ACETYL-INDAN-2-YL)-4-FLUORO-BENZAMIDE

2.87 g (21.6mmol) aluminium trichloride were suspended in 10 ml 1,2-dichloroethane, 500 mg (4.9 mmol) acetic anhydride and 1.0 g N-(indan-2-yl)-4-fluoro-benzamide added, and

the whole was stirred for 2h at RT. The resulting mixture was poured onto ice water/HCl, extracted with dichloromethane, the organic phase was dried with Na_2SO_4 and evaporated.
yield:1.0 g (85%) mp.: 148°C
There were obtained in an analogous way:

EX 192: N-(5-BENZOYL-INDAN-2-YL)-4-FLUORO-BENZAMIDE
mp.: 65°C

EX 193: N-[5-(3-DIMETHYLAMINO-PROPIONYL)-INDAN-2-YL]-4-FLUORO-BENZAMIDE - TRIFLUOROACETATE
340 mg (0.58 mmol) N-(5-acetyl-indan-2-yl)-4-fluoro-benzamide were dissolved in 20 ml dry ethanol, 0.1 ml conc. HCl, then 150 mg (1.74 mmol) N,N-dimethylmethylene-ammoniumchloride were added, before the mixture was heated under reflux, for 8h. The thus-obtained mixture was poured onto water, extracted with ethyl acetate, and the residue obtained after evaporation was fractionated by means of prep. HPLC (RP18, acetonitrile/water, 1% trifluoroacetic acid).
yield: 90 mg of a colourless oil (17%)
^1H (d6-DMSO, 300MHz): 2.86 (s, 6H, $N(CH_3)_2$) 3.0-3.1 (m, 2H, $-CH_2-$), 3.3-3.4 (m, 2H, $-CH_2-$), 3.4-3.5 (m, 2H, $-CH_2-$), 3.5-3.58 (m, 2H, $-CH_2-$), 4.75 (sextett, 1H CH-N), 7.3 (t, 2H, $H^{Phenylen}$), 7.45(d, 1H, H^7), 7.85 (d,1H, H^6), 7.90 (s,1H, H^4), 7.90-8.00 (m, 2H, $H^{Phenylen}$)

EX 194: 4-FLUORO-N-[5-(1-HYDROXY-ETHYL)-INDAN-2-YL]-BENZAMIDE
400 mg (1.35 mmol) N-(5-acetyl-indan-2-yl)-4-fluoro-benzamide were dissolved in 10ml of methanol, then 100mg (2.7mmol) sodium borohydride were added. The mixture was worked up by dropping onto ice/HCl, the resulting solid was filtered off.
yield: 300mg (74%), mp.: 135°C

There were obtained, in an analogous way:

EX 195: 4-FLUORO-N-[5-(HYDROXY-PHENYL-METHYL)-INDAN-2-YL]-BENZAMIDE
mp.: 70°C

EX 196: 4-FLUORO-N-(5-HYDROXY-INDAN-2-YL)-BENZAMIDE
1.45g (5.08mmol) 4-fluoro-N-(5-methoxy-indan-2-yl)-benzamide were dissolved in 50 ml of dichloromethane, 13 ml (12.7 mmol) boron tribromide (1M in dichloromethane) were

added, the whole was stirred for 30 min at RT. The resulting mixture was poured onto 200ml of ice water, the organic phase was washed twice with water, dried, evaporated and the residue obtained was subjected to chromatography on silica with a mixture of dichloromethane/methanol 98:2.

yield: 200mg (16%), mp.: 199°C

EX 197: BENZENESULFONIC ACID 2-(4-FLUOROBENZOYLAMINO)-INDAN-5-YL ESTER

95 mg (0.35mmol) 4-fluoro-N-(5-hydroxy-indan-2-yl)-benzamide were dissolved in 2ml of pyridine, 120 mg (0.72mmol) of benzenesulfonic acid chloride were added, and the mixture was stirred for 5h at 70°C.

The mixture was dropped onto ice water extracted with ethyl acetate. The residue obtained after drying with Na_2SO_4 was subjected to chromatography on silica with a mixture of dichloromethane/methanol 98:2.

yield: 40mg (41%)

^1H (d6-DMSO, 300MHz): 2.91 (dd, 2H, $-CH_2-$), 3.22 (dd, 2H, $-CH_2-$), 4.70 (sextett, 1H CH-N), , 6.75 (dd, 1H, H^6), 6.95 (d,1H, H^4), 7.20 (d,1H, H^7), 7.28 (t, 2H, $H^{Phenylen}$), 7.68 (t, 2H, H^{Phenyl}), 7.80-7.95 (m, 4H, $H^{Phenylen}$ und H^{Phenyl}), 8.68 (d, NH)

There was obtained, in an analogous way:

EX 198: METHANESULFONIC ACID 2-(4-FLUOROBENZOYLAMINO)-INDAN-5-YL ESTER

^1H (d6-DMSO, 300MHz): 2.98 (dd, 2H, $-CH_2-$), 3.28 (dd, 2H, $-CH_2-$), 3.38 (s, 3H, CH_3) 4.73 (sextett, 1H CH-N), 7.16 (dd, 1H, H^6), 7.23 (d,1H, H^4), 7.25-7.35 (m,3H, H^7 + $H^{Phenylen}$), 7.95 (ABdd, 2H, $H^{Phenylen}$), 8.70 (d, NH)

Measurement of activation of eNOS transcription

Activation of eNOS transcription was measured as described in detail in Li et al. "Activation of protein kinase C alpha and/or epsilon enhances transcription of the human endothelial nitric oxide synthase gene", Mol. Pharmacol. 1998; 53: 630-637.

Briefly, a 3,5kB long fragment 5' of the starting codon of the eNOS gene was cloned, sequenced and cloned in firefly luciferase expression plasmids to monitor activation of the eNOS promoter by reporter gene activity. A human endothelial cell line stable transfected

and expressing this promoter-reporter construct was used for compound testing. Cells were incubated for 18h with compounds.

All compounds were dissolved before in sterile DMSO. A final concentration of 0.5% DMSO in complete medium was allowed. Induction of reporter gene expression in these cells was measured using a standard luciferase assay system (Promega, Cat. No E150) according to the manufacturer's instructions. Luciferase induction in cells incubated with compounds were compared to those incubated with solvent alone. The ratio of both activities (transcription induction ratio, TIR) was plotted as a function of compound concentration. Typically, TIR values started at low concentrations at a ratio of 1, indicating no compound effect, and extended up to a maximum TIR value TIR(max) which indicates the increase of the eNOS transcription. EC_{50} values of transcription induction ratios as a function of compound concentration were determined graphically.

The effect of compounds on eNOS-transcription were confirmed in a second assay based on eNOS protein detection. Primary human umbilical vein cord endothelial cells (HUVEC) were isolated and cultivated according to standard procedures. Confluent cells were incubated with compounds for 18h and the effect on eNOS protein expression determined by a quantitative Westernblotting procedure. After compounds incubation, HUVEC were lysed in ice-cold lysis buffer containing 10mM Tris-HCl, pH 8.0, 1% SDS and protease inhibitors. The lysate was subjected to a standard denaturating polyacrylamid gel electropheresis and blotted to nitrocellulose membranes. Using a specific primary monoclonal antibody (Transduction Laboratories, UK) and alkaline phosphatase labelled secondary antibody (Jackson Labs), a specific eNOS protein band was visualized and quantified based on a chemifluorescence detection method.

The results are shown in the table below.

Compound No:	EC-50 (µM)	TIR(max)
1a	6.0	2.80
1b	0.2	3.00
4	3.0	2.95
5	30.0	2.50
6	1.2	2.55
7	0.1	2.57
8	8.0	2.20

Compound No:	EC-50 (μM)	TIR(max)
18	0.8	4.10
19	7.0	2.10
20	5.0	2.20
21	2.5	2.88
22	12.0	2.70
23	0.9	3.80
24	0.2	3.60
25	2.5	4.40
26	0.8	3.80
27	3.0	2.94
28	6.0	3.05
29	1.7	4.00
30	4.0	3.30
31	1.7	3.40
58	0.7	2.60
66	0.4	4.20
70	0.7	4.00
189 a	0.6	3.55
190 b	30.0	3.46
196	12.0	3.50
197	30.0	2.80

Animal Models

All animal experiments were performed in accordance to the German animal protection law and to the guidelines for the use of experimental animals as given by the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health.

Animals and Treatment (Experiments A - C)

ApoE and eNOS deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) were used. All animals were 10 – 12 weeks of age and weighed 22 to 28 g. Three days before surgery mice were divided into 4 groups (apoE control, n=10-12; apoE with test

compounds, n=10-12; eNOS control, n=10-12; eNOS with test compounds, n=10-12) and received either a standard rodent chow (containing 4 % fat and 0,001 % cholesterol; in the following designated as placebo group) or a standard rodent chow + test compound (10 or 30 mg/kg/d p.o.).

A Anti-hypertensive effect in ApoE knockout mice

Blood-pressure was determined in conscious mice using a computerized tail-cuff system (Visitech Systems, Apex, Nc). After treatment of ApoE deficient mice and eNOS deficient mice with the test compounds the blood pressure was compared to the results obtained with a placebo treatment.

For compound 18, after 4 months treatment of ApoE deficient mice blood pressure was significantly ($p<0.05$) lowered in the 30 mg/kg/d group compared to placebo treatment (92 ± 5 mmHg versus 115 ± 2 mmHg). No blood pressure reduction could be observed at similar dosing in eNOS deficient mice after 4 weeks treatment.

B Inhibition of neointima formation and atherogenesis (femoral artery cuff)

After 3 day treatment of ApoE deficient mice with the respective compound, (10mg/kg/d pressed in chow), animals were anesthetized with an intraperitoneal injection of pentobarbital (60 mg/kg) followed by an intramuscular injection of xylazin (2 mg/kg) and a cuff was placed around the femoral artery as described in Moroi et al.(J Clin Invest. 101:1225-32, 1998). Briefly, the left femoral artery was dissected. A non-occlusive 2,0 mm polyethylene cuff made of PE-50 tubing (inner diameter 0,56 mm, outer diameter 0,965 mm, Becton Dickinson, Mountain View, Ca) was placed around the artery and tied in place with two 7-0 sutures. The right femoral artery was isolated from the surrounding tissues but a cuff was not placed. Treatment with the respective compound was continued for 14 days after surgery. Then the animals were sacrificed. The aorta were taken for determination of vascular eNOS expressions by quantitative western blotting. Both femoral arteries were harvested, fixed in formalin and embedded in paraffin. 20 cross sections (10 µm) were cut from the cuffed portion of the left femoral artery and from the corresponding segment of the right artery. Sections were subjected to standard hematoxylin and eosin staining. Morphometric analyses were performed using an image analysis computer program (LeicaQWin, Leica Imaging Systems, Cambridge, GB). For each cross section the area of the lumen, the neointima and the media were determined. To this end, the neointima was defined as the area between the lumen and the internal elastic lamina and

the media was defined as the area between the internal and the external elastic lamina. The ratio between the area of the neointima and the area of the media was expressed as the neointima/media ratio.

The compounds according to the present invention reduce the maladaptive neo-intima formation in this model. Compound 18 reduced the neo-intima formation by a factor of 2, decreasing the neointima to media ratio from 0.39 ± 0.07 in the placebo group to 0.170 ± 0.04 in the compound group. In parallel, vascular eNOS expression was enhanced by a factor of 2.1. No effect of the compounds according to the present invention could be demonstrated in a similar setup using eNOS deficient mice instead of ApoE knockout mice.

C Prevention of atherosclerotic plaque formation in chronic treatment

ApoE deficient mice were treated for 16 weeks with the respective compound pressed in chow and finally sacrificed. Aortas were removed from each mouse, fixed in formalin and embedded in paraffin. Plaque formation was measured via lipid lesions formation in the aortas (from aortic arch to diaphragm) and was analyzed by oil red O staining. For quantifying the effect of the respective compound on vascular eNOS expression the femoral arteries were used in this experiment.

The compounds according to the present invention reduce plaque formation. With respect to compound 18, plaque formation was significantly reduced (5.2 ± 1% versus 13.3 ± 2.6 in the placebo group, values in overall plaque size in % of total surface). Vascular eNOS expression was found to be 1.75 fold up-regulated in the treatment group.

D Improvement of coronary function in diseased ApoE deficient mice

Old Male wild-type C57BL/6J mice (Charles River Wiga GmbH, Sulzfeld), and apoE deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) 6 month of age and weighing 28 to 36 g were used in the experiments. Mice were divided into 3 groups (C57BL/6, n=8; apoE control, n=8; apoE with respective compound, n=8) and received for 8 weeks either a standard rodent chow (containing 4 % fat and 0,001 % cholesterol) or a standard rodent chow + respective compound (30 mg/kg/d p.o.).
Mice were anesthetized with sodium pentobarbitone (100 mg/kg i.p.), and the hearts were rapidly excised and placed into ice-cold perfusion buffer. The aorta was cannulated and

connected to a perfusion apparatus (HUGO SACHS ELECTRONICS, Freiburg, Germany) which was started immediately at a constant perfusion pressure of 60 mm Hg. Hearts were perfused in a retrograde fashion with modified Krebs bicarbonate buffer, equilibrated with 95% O_2 and 5 % CO_2 and maintained at 37.5° C.

A beveled small tube (PE 50) was passed through a pulmonary vein into the left ventricle and pulled through the ventricular wall, anchored in the apex by a fluted end, and connected to a tip-micromanometer (Millar 1.4 French). The left atrium was cannulated through the same pulmonary vein and the heart switched to the working mode with a constant preload pressure of 10 mm Hg and an afterload pressure of 60 mm Hg. Aortic outflow and atrial inflow were continuously measured using ultrasonic flow probes (HSE/Transonic Systems Inc.). Coronary flow was calculated as the difference between atrial flow and aortic flow. All hemodynamic data were digitized at a sampling rate of 1000 Hz and recorded with a PC using spezialized software (HEM, Notocord).

Hearts were allowed to stabilize for 30 min. All functional hemodynamic data were measured during steady state, and during volume- and pressure loading.

Left ventricular function curves were constructed by varying pre-load pressure. For acquisition of preload curves, afterload was set at 60 mm Hg and preload was adjusted in 5 mm Hg steps over a range of 5 to 25 mm Hg. Hearts were allowed to stabilize at baseline conditions between pressure- and volume-loading.

Isolated hearts from ApoE deficient animals displayed a lower coronary flow in this setup compared to C57Bl6 wildtype mice (3.6 ml/min versus 4,95 ml/min). Treatment of ApoE deficient animals with the compounds according to the present invention increases coronary flow. They also improve pre-load dependent coronary flow and reduce the incidence of ventricular arrhythmias as an indicator for anti-ischemic efficacy. With respect to compound 18, coronary flow was improved to 5 ml/min comparable to the levels of non-diseased wildtype mice, and the improvement in pre-load dependent coronary flow and the reduction of the incidence of ventricular arrhythmics were also observed.

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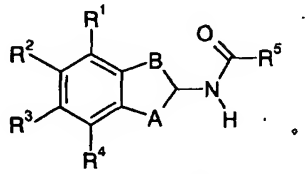
Claims:

1. An acylated indanyl amine according to the general formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein

R^1 and R^4 are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^9CO; $CONR^{10}R^{11}$; $COOR^{12}$; CF_3; halogenes; pseudohalogenes; $NR^{13}R^{14}$; OR^{15}; $S(O)_mR^{16}$; $SO_2NR^{17}R^{18}$; and NO_2;

R^2 and R^3 are independently from each other selected from the group consisting of: H; halogenes; pseudohalogenes; unsubstituted and at least monosubstituted C_1-C_6-alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_6-alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3; CN; NO_2; (C_1-C_6-alkyl)amino; di(C_1-C_6-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH- and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O-; unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1-C_3-alkyl, halogenes and methoxy;

A is CH_2, CHOH or CH-(C_1-C_3-alkyl);

B is CH_2 or CH-(C_1-C_3-alkyl);

R^5 is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogenes; pseudohalogenes; C_1-C_{10}-alkyl; C_3-C_5-alkandiyl; phenyl; phenylsubstituted C_1-C_4-alkyl; CF_3; OH; C_1-C_{10}-alkoxy; phenoxy; benzyloxy; CF_3O; (C_1-C_{10}-alkyl)COO; $S(O)_mR^{20}$; (C_1-C_{10}-alkyl)amino; di(C_1-C_{10}-alkyl)amino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_3-alkyl)-; (C_1-C_{10}-alkyl)-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; phenylamino; phenyl-CO; $COOR^{21}$; $CONR^{22}R^{23}$; $SO_2NR^{24}R^{25}$; and aromatic or aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, O and S which can be substituted by one or more substituents from the group consisting of halogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; wherein all phenyl groups and phenyl-containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3;

R^6 is H, C_1-C_6-alkyl or benzyl;

R^7 is selected from the group consisting of:
H; C_1-C_6-alkyl which can be phenyl-substituted; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

R^8 is H or C_1-C_6-alkyl;

R^9 is C_1-C_6-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogenes, pseudohalogenes, and CF_3;

R^{10} independently has the same meaning as R^7;

R^{11} independently has the same meaning as R^8;

R^{12} independently has the same meaning as R^6;

R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{14} is H or C_1-C_6-alkyl;

R^{15} is selected from the group consisting of: H; C_1-C_6-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{16} is selected from the group consisting of: C_1-C_6-alkyl; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substitutents can be present;

R^{17} independently has the same meaning as R^7;

R^{18} independently has the same meaning as R^8;

R^{19} independently has the same meaning as R^{16};

R^{20} independently has the same meaning as R^{16};

R^{21} independently has the same meaning as R^6;

R^{22} independently has the same meaning as R^7;

R^{23} independently has the same meaning as R^8;

R^{24} independently has the same meaning as R^7;

R^{25} independently has the same meaning as R^8;

heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O and S;

aryl is phenyl, naphth-1-yl or naphth-2-yl;

m is 0, 1 or 2,

with the proviso that, in case R^1, R^2, R^3 and R^4 are all H, R^5 is not phenyl, 5-chloro-2-ethoxyphenyl, 5-chloro-2-methoxyphenyl, 5-bromo-2-methoxyphenyl, or quinoxalin-2-yl; in case R^5 is phenyl, A is not CHOH, R^1 is not methoxy or methyl, R^2 is not methyl or B is not $CH\text{-}CH_3$; in case R^2 is NO_2, R^5 is not 3-chlorophenyl.

2. An acylated indanyl amine or a pharmaceutically acceptable salt thereof according to claim 1, wherein in the formula (I)

R^1 is selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogenes; pseudohalogenes; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms from the group consisting of N, O, and S;

R^2 is selected from the group consisting of: H; halogenes; pseudohalogenes; and C_1-C_3-alkyl;

R^3 and R^4 are each H;

A is selected from the group consisting of CH_2 and CHOH;

B is selected from the group consisting of CH_2 and $CH\text{-}CH_3$;

R^5 is selected from the group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_3-alkyl)amino-, di(C_1-C_3-alkyl)amino, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -OCH_2-CH_2-O-; unsubstituted and at least mono-halogene-substituted benzodioxolyl and dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, –O-CH_2-O-, –O-CF_2-O-, and -O-CH_2-CH_2-O-; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -O-CH_2-CH_2-O-, where heteroaryl is selected from the group consisting of 5- to 10-membered mono- or bicyclic aromatic heterocycles containing one or more heteroatoms from the group consisting of N, O, and S;

m is 0 or 2.

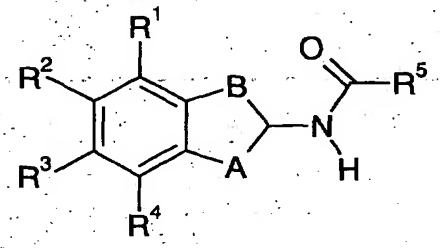
3. An acylated indanyl amine or a pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein in the formula (I)
R^1 is H, halogene or C_1-C_4-alkyl;

A is CH_2;

R^5 is in particular selected from the group consisting of: 4-fluorophenyl; 4-chlorophenyl; 4-bromophenyl; 4-(C_1-C_3-alkyloxy)-phenyl; 4-trifluoromethoxyphenyl; 2-bromo-4-fluorophenyl; 2-chloro-4-fluorophenyl; 3,4-dimethylphenyl; 2,4-dimethylphenyl; 4-chloro-2-methylphenyl; 2-hydroxy-4-methylphenyl; 2-hydroxy-4-ethoxyphenyl; 2-methoxy-4-methylphenyl; 4-phenoxyphenyl; 3-fluoro-4-methylphenyl; benzo[1,3]dioxol-5-yl; 2,2-difluoro-benzo[1,3]dioxol-5-yl; 2,3-dihydrobenzofuran-5-yl; thienyl; halogene-substituted thienyl; 5-acetylthienyl; pyridyl; halogene-substituted pyridyl; and (C_1-C_3-alkyl)-substituted pyridyl;

heteroaryl is selected from the group consisting of furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

4. An acylated indanyl amine according to the general formula (I)



I

wherein

R^1 and R^4 are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^9CO; $CONR^{10}R^{11}$; $COOR^{12}$; CF_3; halogenes; pseudohalogenes; $NR^{13}R^{14}$; OR^{15}; $S(O)_mR^{16}$; $SO_2NR^{17}R^{18}$; and NO_2;

R^2 and R^3 are independently from each other selected from the group consisting of: H; halogenes; pseudohalogenes; unsubstituted and at least monosubstituted C_1-C_6-alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_6-alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3, CN; NO_2; (C_1-C_6-alkyl)amino; di(C_1-C_6-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH- and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O-; unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part

of which can be substituted by one or more substituents from the group consisting of C_1-C_3-alkyl, halogenes and methoxy;

A is CH_2, CHOH or CH-(C_1-C_3-alkyl);

B is CH_2 or CH-(C_1-C_3-alkyl);

R^5 is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogenes; pseudohalogenes; C_1-C_{10}-alkyl; C_3-C_5-alkandiyl; phenyl; phenylsubstituted C_1-C_4-alkyl; CF_3; OH; C_1-C_{10}-alkoxy; phenoxy; benzyloxy; CF_3O; (C_1-C_{10}-alkyl)COO; $S(O)_mR^{20}$; (C_1-C_{10}-alkyl)amino; di(C_1-C_{10}-alkyl)amino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_3-alkyl)-; (C_1-C_{10}-alkyl)-CO; CF_3-CO; $-OCH_2O-$; $-OCF_2O-$; $-OCH_2CH_2O-$; $-CH_2CH_2O-$; phenylamino; phenyl-CO; $COOR^{21}$; $CONR^{22}R^{23}$; $SO_2NR^{24}R^{25}$; and aromatic or aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, O and S which can be substituted by one or more substituents from the group consisting of halogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; wherein all phenyl groups and phenyl-containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3;

R^6 is H, C_1-C_6-alkyl or benzyl;

R^7 is selected from the group consisting of:
H; C_1-C_6-alkyl which can be phenyl-substituted; phenyl; indanyl; and heteroaryl, and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

R^8 is H or C_1-C_6-alkyl;

R^9 is C_1-C_6-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substitu ents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogenes, pseudohalogenes, and CF_3;

R^{10} independently has the same meaning as R^7;

R^{11} independently has the same meaning as R^8;

R^{12} independently has the same meaning as R^6;

R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{14} is H or C_1-C_6-alkyl;

R^{15} is selected from the group consisting of: H; C_1-C_6-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

R^{16} is selected from the group consisting of: C_1-C_6-alkyl; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substitutents can be present;

R^{17} independently has the same meaning as R^7;

R^{18} independently has the same meaning as R^8;

R^{19} independently has the same meaning as R^{16};

R^{20} independently has the same meaning as R^{16};

R^{21} independently has the same meaning as R^6;

R^{22} independently has the same meaning as R^7;

R^{23} independently has the same meaning as R^8;

R^{24} independently has the same meaning as R^7;

R^{25} independently has the same meaning as R^8;

heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O and S;

aryl is phenyl, naphth-1-yl or naphth-2-yl;

m is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof,

for use as pharmaceutical.

5. An acylated indanyl amine or a pharmaceutically acceptable salt thereof for use as pharmaceutical according to claim 4, wherein in the formula (I)

R^1 is selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogenes; pseudohalogenes; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms from the group consisting of N, O, and S;

R^2 is selected from the group consisting of: H; halogenes; pseudohalogenes; and C_1-C_3-alkyl;

R^3 and R^4 are each H;

A is selected from the group consisting of CH_2 and CHOH;

B is selected from the group consisting of CH_2 and CH-CH_3;

R^5 is selected from the group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_3-alkyl)amino-, di(C_1-C_3-alkyl)amino, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -O-CH_2-CH_2-O-; unsubstituted and at least mono-halogene-substituted benzodioxolyl and dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, –O-CH_2-O-, –O-CF_2-O-, and -O-CH_2-CH_2-O-; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -O-CH_2-CH_2-O-, where heteroaryl is selected from the group consisting of 5- to 10-membered mono- or bicyclic aromatic heterocycles containing one or more heteroatoms from the group consisting of N, O, and S;

m is 0 or 2.

6. An acylated indanyl amine or a pharmaceutically acceptable salt thereof for use as pharmaceutical according to claim 4 or 5, wherein in the formula (I)

R^1 is halogene or C_1-C_4-alkyl,

A is CH_2;

R^5 is in particular selected from the group consisting of: 4-fluorophenyl; 4-chlorophenyl; 4-bromophenyl; 4-(C_1-C_3-alkyloxy)-phenyl; 4-trifluoromethoxyphenyl; 2-bromo-4-fluorophenyl; 2-chloro-4-fluorophenyl; 3,4-dimethylphenyl; 2,4-dimethylphenyl; 4-chloro-2-methylphenyl; 2-hydroxy-4-methylphenyl; 2-hydroxy-4-ethoxyphenyl; 2-methoxy-4-methylphenyl; 4-phenoxyphenyl; 3-fluoro-4-methylphenyl; benzo[1,3]dioxol-5-yl; 2,2-difluoro-benzo[1,3]dioxol-5-yl; 2,3-dihydrobenzofuran-5-yl; thienyl; halogene-substituted thienyl; 5-acetylthienyl; pyridyl; halogene-substituted pyridyl; and (C_1-C_3-alkyl)-substituted pyridyl;

heteroaryl is selected from the group consisting of furyl, pyrroloyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

7. The use of a compound as defined in any of the claims 4 to 6 for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase.

8. The use of a compound as defined in any of the claims 4 to 6 for the manufacture of a medicament for the treatment of cardiovascular diseases, stable and unstable angina pectoris, coronary heart disease, Prinzmetal angina, acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension, essential hypertension, pulmonary hypertension, secondary hypertension, renovascular hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes and diabetes complications, nephropathy and retinopathy, angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, and restricted memory performance or a restricted ability to learn, or the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptiva.

9. A pharmaceutical preparation comprising an effective dose of at least one compound of the formula (I) as defined in any of claims 4 to 6 and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10. A method for the synthesis of a compound according to the general formula (I) wherein R^1, R^2, R^3, R^4 and R^5 and A and B have the meaning defined in claim 1, which method comprises the coupling reaction of the respective indanyl amine with an appropriate acid or acid chloride in the presence of an appropriate base and/or an appropriate coupling agent, optionally followed by a functionalization of the thus-obtained compound.

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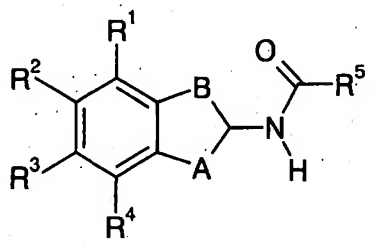
13. Feb. 2001

Aventis Pharma Deutschland GmbH

February 13, 2001
APD61815EP IB/HN/AEW/uw

Abstract

The present invention relates to acylated indanyl amines according to the general formula (I) and their pharmaceutically acceptable salts, for use as pharmaceuticals.



(I)

The substituents R^1 to R^5 have in particular the following meanings: R^1 is selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogenes; pseudohalogenes; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms from the group consisting of N, O, and S; R^2 is selected from the group consisting of: H; halogenes; pseudohalogenes; and C_1-C_3-alkyl; R^3 and R^4 are each H; A is selected from the group consisting of CH_2 and CHOH; B is selected from the group consisting of CH_2 and CH-CH_3; R^5 is selected from the group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_3-alkyl)amino-, di(C_1-C_3-alkyl)amino, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -OCH_2-CH_2-O-; unsubstituted and at least mono-halogene-substituted benzodioxolyl and dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-alkyl)-$S(O)_m$-, phenylmercapto, –O-CH_2-O-, –O-CF_2-O-, and -O-CH_2-CH_2-O-; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1-C_6-alkyl, CF_3, C_1-C_6-alkoxy, trifluoromethoxy, phenoxy, (C_1-C_4-

alkyl)-$S(O)_m$-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH_2-O-, -O-CF_2-O-, and -O-CH_2-CH_2-O-, where heteroaryl is selected from the group consisting of 5- to 10- membered mono- or bicyclic aromatic heterocycles containing one or more heteroatoms from the group consisting of N, O, and S; m is 0 or 2.

The compounds are useful for the manufacture of medicaments for the treatment of cardiovascular diseases, stable and unstable angina pectoris, coronary heart disease, Prinzmetal angina, acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension, essential hypertension, pulmonary hypertension, secondary hypertension, renovascular hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes and diabetes complications, nephropathy and retinopathy, angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, and restricted memory performance or a restricted ability to learn, or the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptiva.